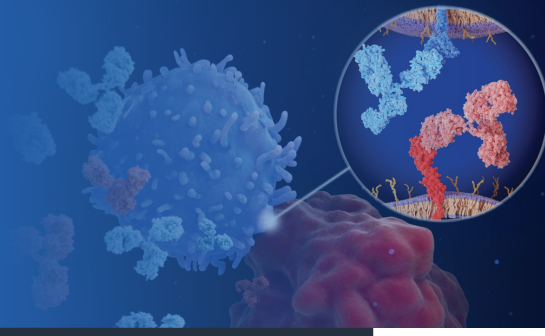
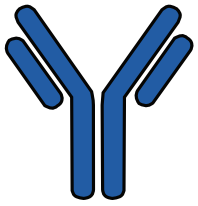
Monitoring and Managing Immune-Related Adverse Events for Pharmacists

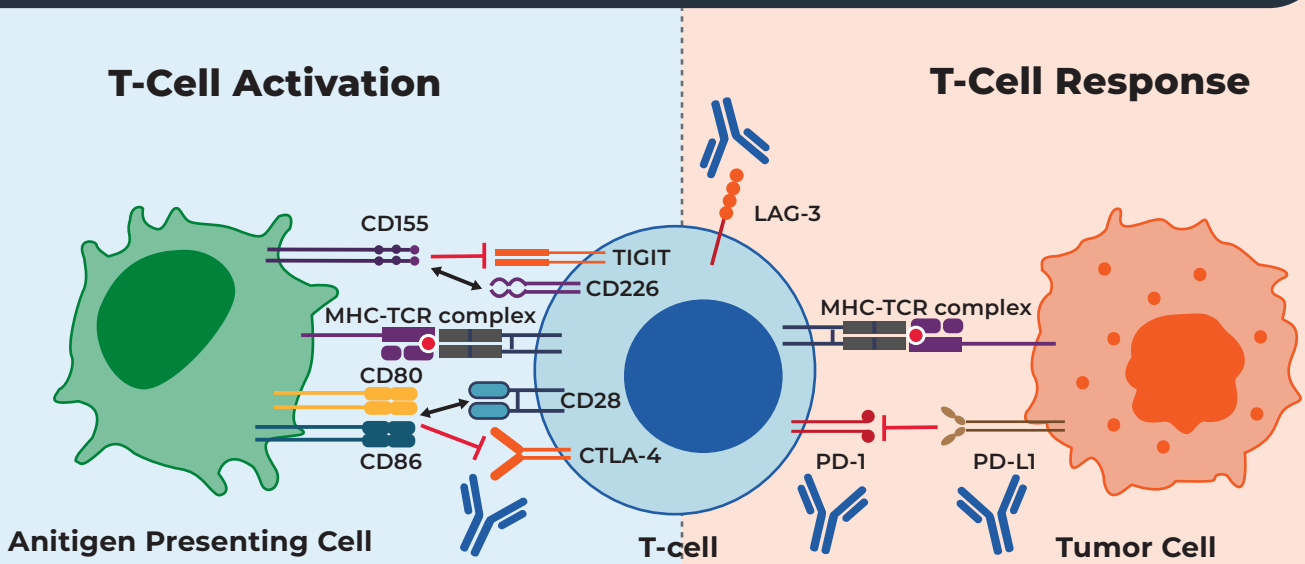


Immune Checkpoint Inhibitors: Mechanisms of Action[1]



- Immune checkpoints function to stop T-cells from attacking healthy tissues during immune activation.
- Some tumors avoid immune system attacks by expressing immune checkpoint proteins on their cell surface.
- Immune checkpoint inhibitors (ICIs) prevent immune checkpoint proteins on tumor cells from binding checkpoint receptors on the surface of T-cells, allowing the activation of an antitumor response.

Mechanism of Action of Immune Checkpoint Inhibitors[2]



FDA-Approved Immune Checkpoint Inhibitors and Targets[3-12]

CTLA-4	LAG-3	PD-1	PD-L1
Ipilimumab, tremelimumab*	Relatlimab†	Cemiplimab, dostarlimab, nivolumab, pembrolizumab, retifanlimab	Atezolizumab, avelumab, durvalumab

*Approved in combination with durvalumab. †Approved in combination with nivolumab.

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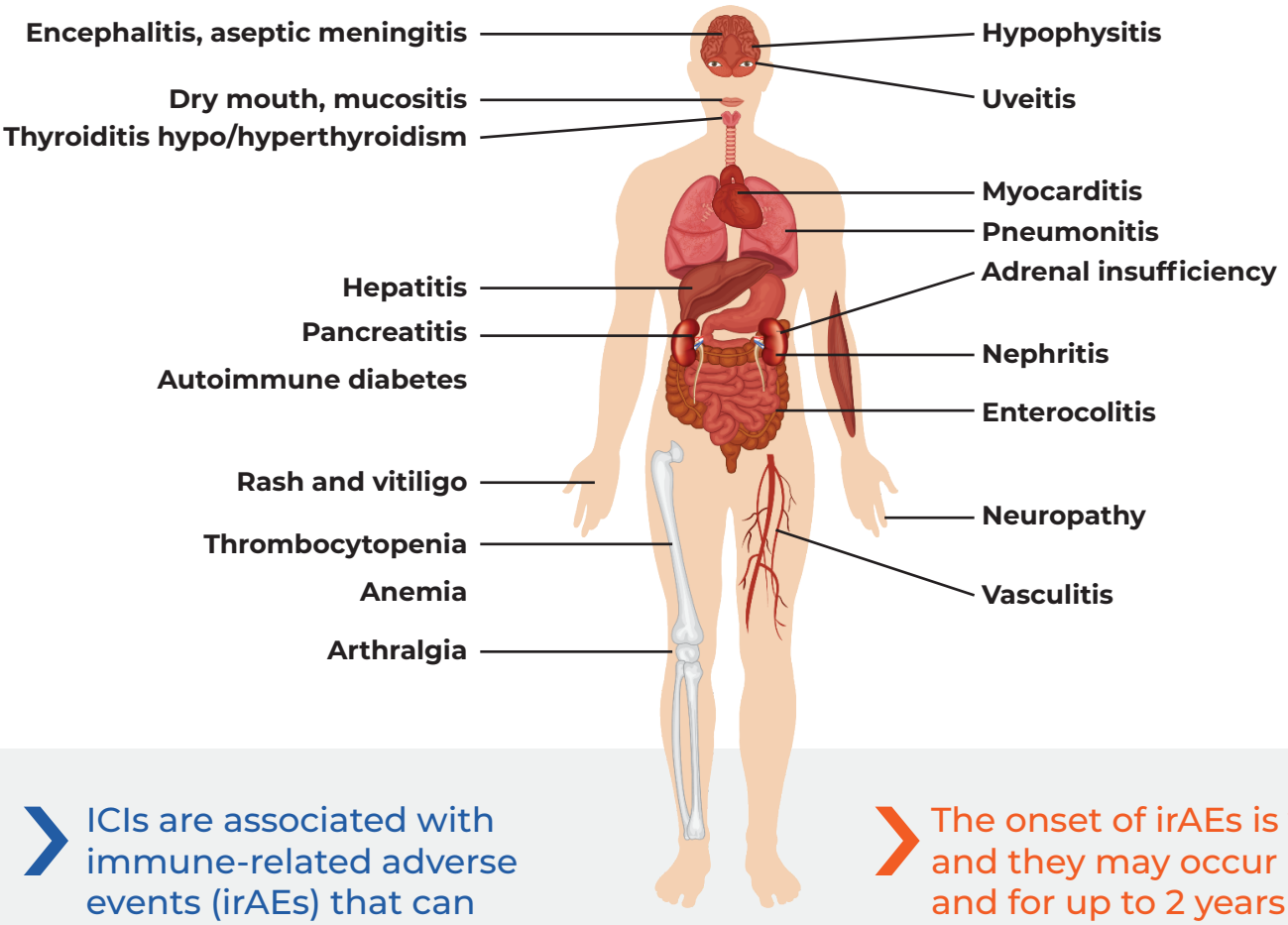
Spectrum of irAEs With Immune Checkpoint Inhibitors[13-15]

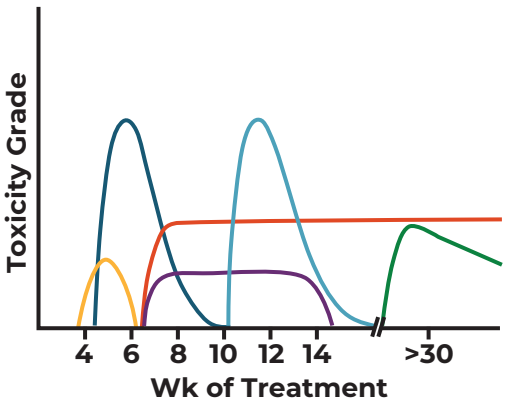


ICIs are associated with immune-related adverse events (irAEs) that can affect any body system.

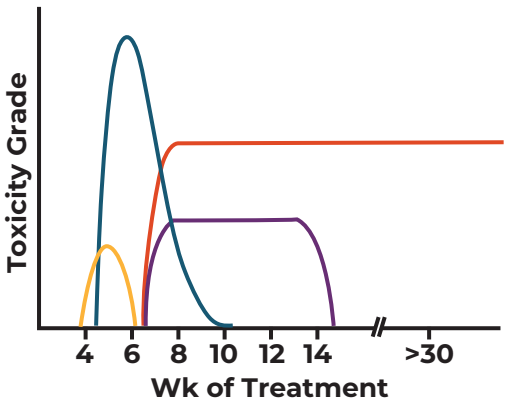
The onset of irAEs is variable, and they may occur at any time and for up to 2 years after the completion of ICI therapy.[16,17]

Timing of irAEs[16]

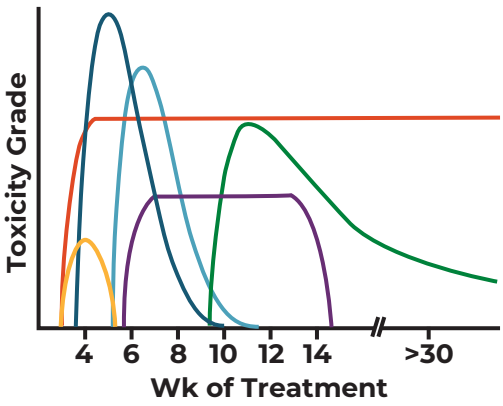
irAE Kinetics With PD-1/PD-L1 Antibodies



irAE Kinetics With CLTA-4 Inhibitor Ipilimumab

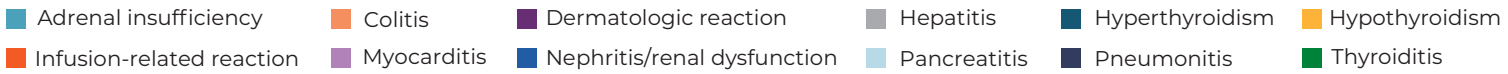


irAE Kinetics of Ipilimumab With an Anti–PD–1 Antibody

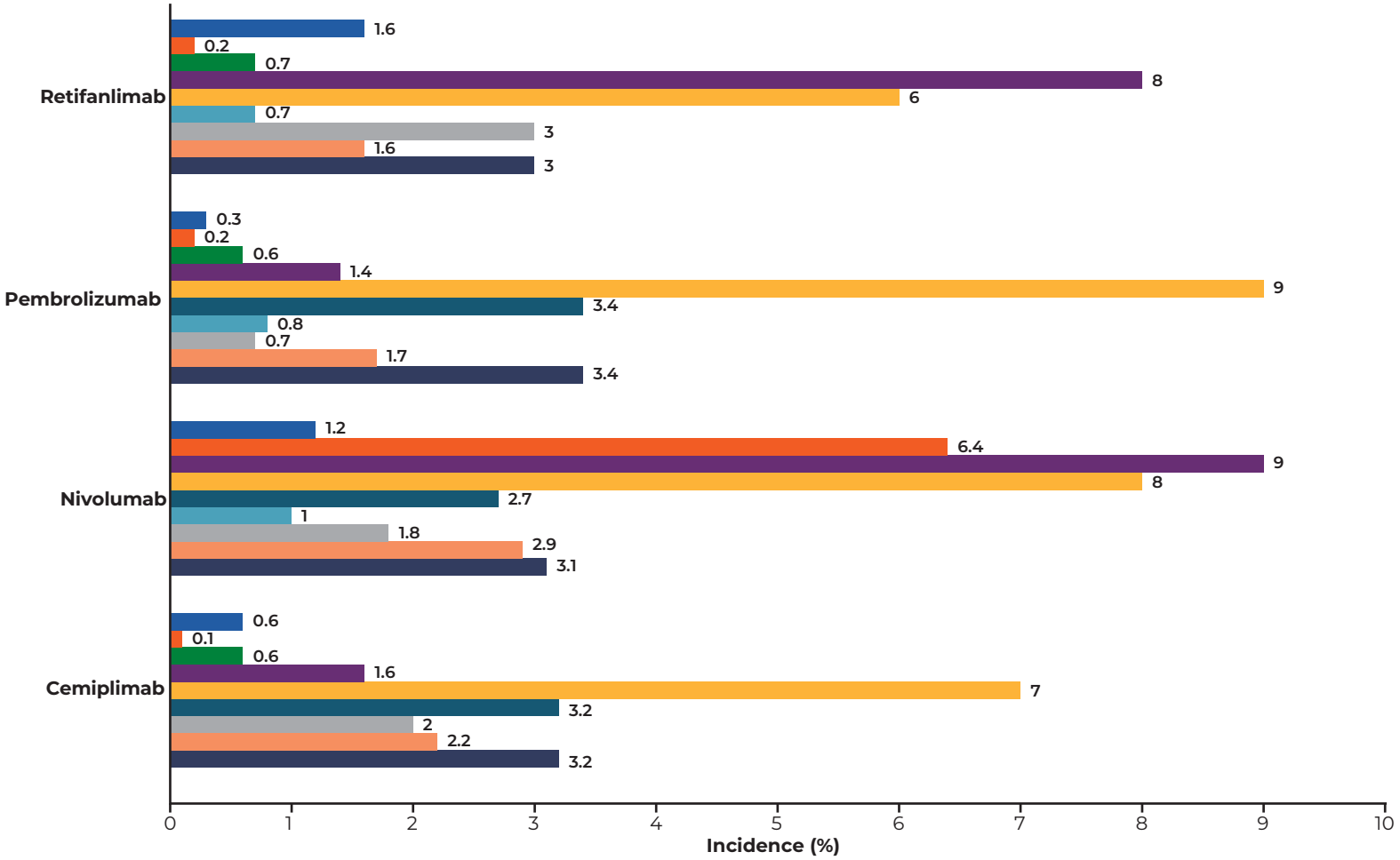


Colitis
Endocrinopathy
Nephritis
Liver toxicity
Skin rash or pruritus
Pneumonitis

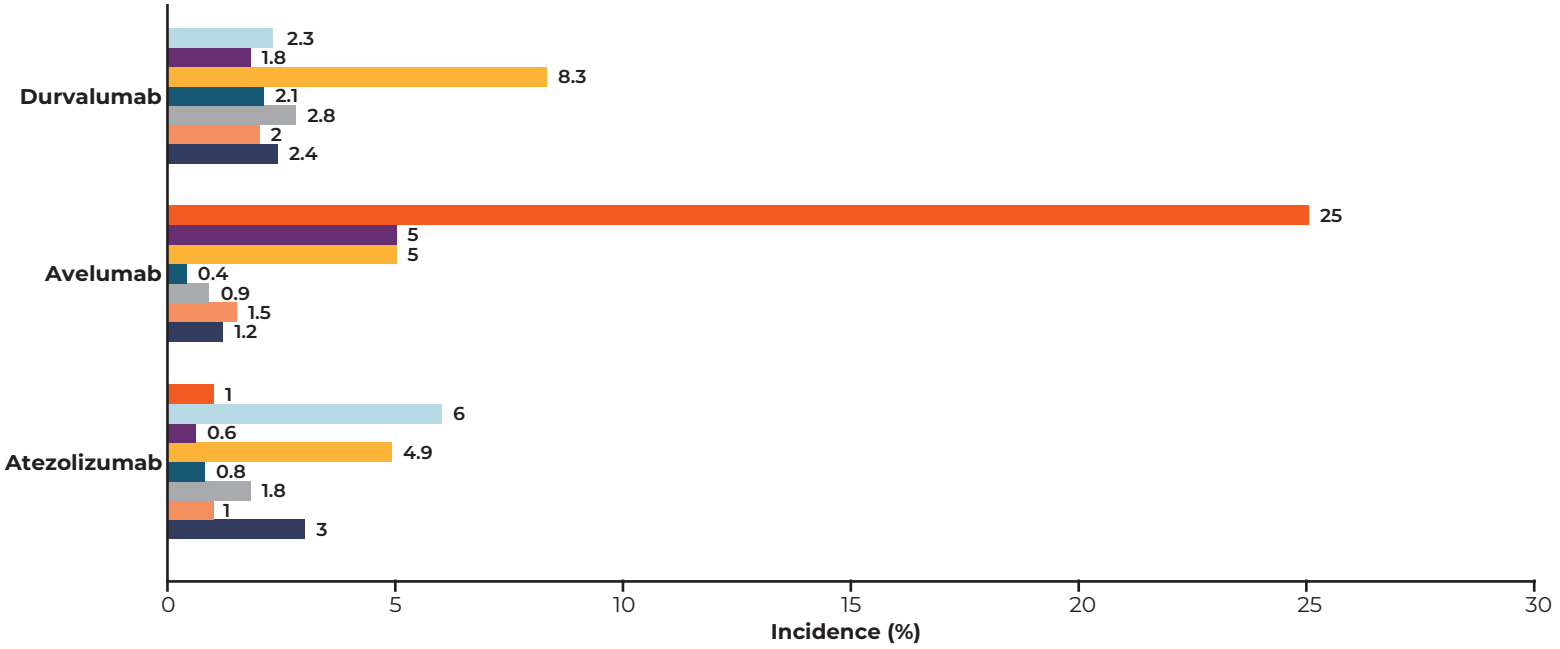
Incidence of Common irAEs (Any Grade) With FDA-Approved Immune Checkpoint Inhibitors[3-12]



PD-1 Inhibitors

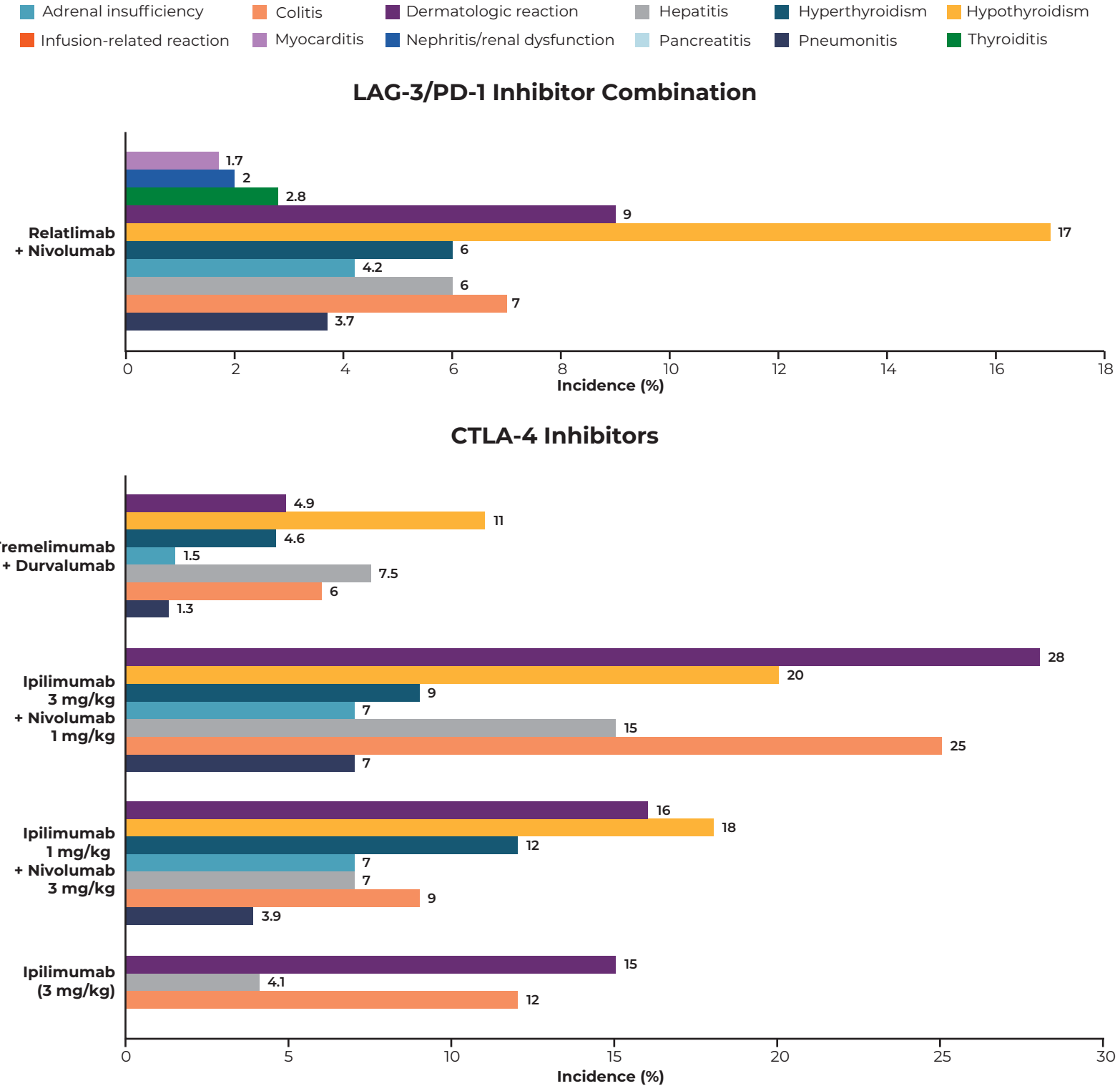


PD-L1 Inhibitors



Missing values for individual AEs on this graph were not reported. Other irAEs may have occurred at an incidence <1%.

Incidence of Common irAEs (Any Grade) With FDA-Approved Immune Checkpoint Inhibitors (cont'd)[3-12]



Missing values for individual AEs on this graph were not reported. Other irAEs may have occurred at an incidence <1%.

The incidence of irAEs varies by agent and may differ when ICIs are used in combination.

Monitoring for irAEs[18,19]

Most irAEs can be managed effectively through early detection and treatment.

Regular monitoring through physical examinations and blood testing should be conducted before starting ICI therapy, before each cycle, and following the end of ICI therapy to help detect irAEs.

Here is a general overview of recommended monitoring approaches and intervals for the detection of irAEs.

Assessment	Monitoring
Clinical	• Pretherapy assessment should include physical and neurologic examinations, patient and family history to assess for organ-specific diseases, autoimmune diseases, infectious diseases, as well as the potential for drug–drug interactions with ICI therapy • Conduct at each visit along with assessment of AEs of therapy (eg, changes in gastrointestinal and lung function)
General bloodwork (ie, complete blood count, comprehensive metabolic panel)	• Assess pretherapy and repeat before each ICI treatment or every 4 weeks during ICI therapy, and then every 6-12 weeks or as indicated
Dermatologic assessment	• Perform pretherapy skin and mucosal examination if there is history of immune-related skin disorders • Perform skin and mucosal examination as needed following initiation of ICI therapy
Pancreatic	• Baseline testing is not required • Routine testing is not needed for asymptomatic patients
Thyroid assessment	• Assess thyroid-stimulating hormone (TSH) and free thyroxine (T4) before therapy • Evaluate TSH and T4 every 4-6 weeks during ICI therapy and every 12 weeks thereafter as indicated
Pituitary/adrenal	• Consider baseline morning serum cortisol measurements • Consider repeating every 4-6 weeks during ICI therapy and every 12 weeks thereafter as indicated
Pulmonary assessment	• Assess pretherapy oxygen saturation level and consider pulmonary function testing for high-risk patients • Repeat oxygen saturation testing during ICI therapy and follow-up based on symptoms
Cardiovascular	• Consider baseline ECG, troponin level, and cardiology consult with individualized assessment • If baseline ECG is abnormal or symptoms are present, consider periodic testing
Musculoskeletal	• Perform pretherapy assessment as needed for those with preexisting disease • Routine monitoring is not needed for asymptomatic patients

Patients receiving combination immunotherapy regimens may need more frequent monitoring for irAEs.

Grade and Management Recommendation*

1 (mild)	2 (mild to moderate)	3 (moderate to severe)	4 (severe or life-threatening)
Symptomatic management			
• Continue therapy (exceptions: pulmonary, cardiac, neurologic, or hematologic irAEs may require discontinuation)	• Hold ICI for most grade 2 until resolution to grade 1; consider rechallenge after resolution; permanently discontinue if reaction reoccurs • Initiate corticosteroids (eg, prednisone 0.5-1.0 mg/kg/day)	• Initiate high-dose corticosteroids (eg, prednisone 1-2 mg/kg/day); taper steroids over 4-6 weeks • Hold ICI • At resolution to grade ≤1, cautious rechallenge with ICI, especially in patients with early development of irAE	• Corticosteroids as in grade 3 • Permanently discontinue ICI, except for endocrinopathies controlled with hormone replacement

*Consult prescribing information for detailed recommendations.

- **Patients who experience grade 3/4 endocrine toxicities may resume ICI therapy after stabilization on appropriate hormone supplementation.[19]**
- **For patients receiving a PD-1/PD-L1 inhibitor and a CTLA-4 inhibitor who develop grade ≥2 diarrhea/colitis, consider permanently discontinuing the CTLA-4 inhibitor and resuming the PD-1/PD-L1 inhibitor.[19]**
- **Patients restarting immunotherapy after significant irAEs should be monitored carefully. If toxicity occurs on rechallenge, the treatment should be permanently discontinued.**

Supportive Care for irAEs[18,20]

AE	Symptomatic Supportive Care Measures
Rash/pruritus	• Topical emollients and/or topical corticosteroids • Moderate- to high-potency topical corticosteroids may be used as appropriate • Oral antihistamines for pruritus • Consider gabapentinoids or dupilumab, omalizumab, or narrow-band UVB phototherapy for moderate to severe pruritus
Diarrhea/colitis	• Loperamide or diphenoxylate/atropine for grade 1 diarrhea only; not recommended for patients with colitis-related symptoms
Endocrine toxicities Hyperthyroidism	• β-blocker for symptomatic • Consider additional therapies for grade 3/4 (eg, corticosteroids, methimazole)
Hypothyroidism	• Thyroid hormone supplementation
Hypophysitis/ adrenal insufficiency	• Hydrocortisone replacement • Medical alert bracelet • Stress-dose steroids as needed
Musculoskeletal	• Analgesia with acetaminophen and/or NSAIDs, unless contraindicated

NSAID, nonsteroidal anti-inflammatory drug.

Management and Prevention Recommendation

Pretreatment considerations

- Baseline should include screening for hepatitis B/C, latent or active tuberculosis, and viral load and CD4+ cell count in patients with HIV
- Preexisting comorbid conditions (eg, diabetes, hypertension, glaucoma, infection) should be managed as best as possible before starting steroid treatment
- Use the lowest dose and shortest duration of steroid treatment needed to control irAEs

Preventing opportunistic infections

- Consider *Pneumocystis jirovecii* pneumonia prophylaxis for patients receiving ≥20 mg/day for ≥4 weeks or >30 mg for ≥3 weeks
- Follow institutional guidelines for prophylactic fluconazole with steroid use >12 weeks
- Herpes zoster prophylaxis may be offered to prevent reactivation in patients with prior infection

Acute or short-term steroid-related AEs

- Routinely ask about or monitor for the following short-term steroid-related AEs: infection, insomnia, anxiety, diabetes or glucose intolerance, skin changes

Long-term steroid-related AEs

- Routinely ask about or monitor for the following long-term steroid-related AEs: cataracts or glaucoma, steroid myopathy, relative adrenal insufficiency, gastric or duodenal ulcers, psychiatric disturbance, osteopenia/osteoporosis, fractures
- Advise patients to consume adequate calcium, vitamin D and perform weight-bearing exercises as feasible
- Bone-modifying agents are recommended for those receiving steroids for >3 months and for those with preexisting osteoporosis
- Gastrointestinal prophylaxis with proton pump inhibitors and H2 antagonists is recommended

Tapering steroids

- In general, taper steroids slowly, over 4-6 weeks
- Monitor for irAE rebound or recurrence during taper
- Monitor for symptoms of adrenal insufficiency during taper after prolonged steroid use

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9. Pembrolizumab PI.
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Patient Checklist: When to Call the Doctor

Advise patients to call their provider if they experience any of the following signs and symptoms of irAEs.[3-12]

Lung inflammation

- [ ] New or worsening cough
- [ ] Chest pain
- [ ] Shortness of breath

Intestinal problems

- [ ] Diarrhea or excessive number of bowel movements
- [ ] Blood or mucus in stools or dark, tarry, sticky stools
- [ ] Abdominal pain or tenderness

Liver problems

- [ ] Yellowing of skin or whites of eyes
- [ ] Dark, tea-colored urine
- [ ] Nausea or vomiting
- [ ] Pain on the right side of your abdomen
- [ ] Bleeding or bruising more easily than normal

Skin reactions

- [ ] Skin rash, with or without itching
- [ ] Sores in your mouth
- [ ] Blistered or peeling skin
- [ ] Itching

Nerve problems

- [ ] Unusual weakness of legs, arms, or face
- [ ] Numbness or tingling in hands or feet

Eye inflammation

- [ ] Blurry vision, double vision, or other vision problems
- [ ] Eye pain or redness

Kidney inflammation or failure

- [ ] Decrease in volume of urine
- [ ] Blood in urine
- [ ] Swollen ankles
- [ ] Loss of appetite

Hormone gland problems

- [ ] Persistent or unusual headaches
- [ ] Rapid heartbeat
- [ ] Increased sweating
- [ ] Severe fatigue
- [ ] Weight gain or loss
- [ ] Increased hunger or thirst
- [ ] Urinating more often
- [ ] Feeling cold
- [ ] Severe fatigue
- [ ] Dizziness or fainting
- [ ] Voice gets deeper
- [ ] Changes in mood or behavior
- [ ] Hyperthyroidism (fatigue, hand tremors, mood swings, rapid heartbeat)
- [ ] Hypothyroidism (changes in menstrual cycle, constipation, depression, dry hair/ hair loss, fatigue)

Other problems

- [ ] Severe or persistent muscle or joint pains
- [ ] Severe muscle weakness

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